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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/971,338	11/17/97	LEE	S GDF-1

HM12/0222

EXAMINER

ALLEN, M

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No. 08/971,338	Applicant(s) Lee
Examiner Marianne P. Allen	Group Art Unit 1645

Responsive to communication(s) filed on _____

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 4-10 and 22-33 is/are pending in the application.

Claim(s) 4-10 and 22-33 is/are withdrawn from consideration.

Of the above, claim(s) _____ is/are allowed.

Claim(s) _____ is/are rejected.

Claim(s) 4-10 and 22-33 is/are objected to.

Claim(s) _____ are subject to restriction or election requirement.

Claims _____

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1645.

Examination of this application is resumed following suspension at the request of applicant in order to submit declaration evidence.

Claims 4-10 and 22-33 are under consideration by the examiner.

Claims 4-7, 22, 24-25, and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

These claims are directed to mammalian GDF-1 proteins (claim 4), unspecified GDF-1 proteins (claim 24), and hamster GDF-1 proteins (claim 6). The specification provides the sequences of mouse and human GDF-1. The specification further indicates that they have less conservation across species (69%) than other members of the TGF- β superfamily. (See page 31.) The specification contains no disclosure of the expected structure for other members of this family or what structural features identify a protein as a GDF-1 protein. Furthermore, as the activity of GDF-1 was not known at the time of the invention, the specification does not enable any assays for identification of GDF-1.

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Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the mouse and human sequences, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides (which would be required for recombinant production of the protein) and proteins and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

See also the July 22, 1997, CAFC decision of The Regents of the University of California v. Eli Lilly and Company where generic claims to vertebrate and mammalian insulin cDNA's were

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found to be invalid because of lack of adequate written description where only the rat sequence was disclosed.

Again, although the specification discloses the human and mouse GDF-1 sequences, the specification fails to define the structural features that characterize GDF-1 that would permit one of ordinary skill in the art to recognize the structure of hamster or another mammalian GDF-1.

Claims 4-10 and 22-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 4-10, 22-23, and 31-33 are directed to GDF-1 proteins. Claims 24-30 are directed to methods of purifying GDF-1 proteins.

The specification fails to enable how to use the GDF-1 protein without undue experimentation. Without knowing how to use the end product, the methods of purification (claims 24-30) are also not enabled with respect to how to use. Biological properties are alleged based upon the similarity of the GDF-1 amino acid sequence to the TGF- β family. However, there is no evidence of record that GDF-1 is a biologically useful protein possessing any particular properties. (See specification page 12, lines 8-20.) The similarities between GDF-1 and the TGF- β family members range from 26-52% on the amino acid level and these proteins are not deemed

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to be predictive of the biological properties possessed by GDF-1. The biological activities of the TGF- β family are diverse and it could not have been predicted which activity GDF-1 would have, if any. As such, the specification does not enable using the GDF-1 protein as disclosed in the specification. For example, there is no disclosure of any disease state that can be treated with this protein nor any tumors, genetic diseases, or developmental anomalies that has been associated with this gene or protein. It would require undue experimentation to practice any of these uses. The examiner is unaware of any tumors, genetic diseases, or developmental anomalies that have been associated with this gene or protein even now, well after the effective filing date.

In rebuttal of this position and to establish a biological activity for GDF-1, applicant has submitted the Ebendal declaration under 37 CFR 1.132. This declaration sets forth that recombinant human GDF-1 (amino acids 255-373 fused to 34 additional amino acids) was produced in E. coli and recovered as a dimer. This product potentiates human NT-3 fibre outgrowth. The assays used to establish this biological activity are referenced to Ebendal (1995) and Ernfors (1990). The declaration asserts that this biological activity on neurons is similar to other members of the TGF- β superfamily.

First of all, the particular material tested is not disclosed in the specification. That is, while Figure 11B discloses the human GDF-1 sequence, the portion of this protein and the particular fusion partner used in the declaration experiments do not appear to be disclosed in the specification. Use of the particular pRSET vector by Invitrogen does not appear to be disclosed in the specification. Use of a dimer versus a monomer does not appear to be disclosed in the

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specification. The fibre outgrowth assay of Ebendal et al. (1995) was developed after the effective filing date of the application. The Ernfors et al. (1990) reference is also post-filing date for the ultimate parent application. Furthermore, it discloses fibre outgrowth activity of NT-3 (although not named as such in this reference) but does not disclose similar activity of TGF- β superfamily members or GDF-1 proteins. It is noted that the declaration evidence indicates that GDF-1 alone was ineffective to evoke fibre outgrowth.

It appears that the potentiating activity between the TGF- β superfamily member OP-1 and NT-3 was not known until well after the effective filing date. (See Bengtsson et al., Journal of Neuroscience Research, 1998.) It is noted that the receptors discussed were not known at the time of the invention nor does the reference generally postulate this activity to all other members of the superfamily. The involvement of the GDF family was only determined well after the effective filing date. (See Ebendal et al., Journal of Neuroscience Research, 1998.) It was not discovered until well after the effective filing date that TGF- β 3 potentiates the survival achieved with NT-3 and NT-4. (See Kriegstein et al., Neurochemical Research, 1996.)

Massague provides a review of the TGF- β superfamily at approximately the time of the invention. The reference sets forth the diverse effects of the various members of the superfamily. The potentiating effect of the Ebendal declaration is not disclosed.

For all of these reasons, the Ebendal declaration is not sufficient to overcome the enablement rejection.

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As set forth in the prior Office action, the specification has not informed those skilled in the art how to use the claimed invention. Nothing in the specification as filed would lead one of ordinary skill in the art to evaluating this activity nor associating it with a particular member of the TGF- β superfamily or NT-3. Clearly, the experimentation involved to reach such a discovery was extensive and not routine. Applicant is reminded that the specification is required to clearly state how the claimed invention is to be used. It should be apparent to one of ordinary skill in the art how the claimed invention is to be used after reading the specification. One of ordinary skill in the art should not have to envision, infer, or "dream up" potential uses or perform experimentation requiring such ingenuity, decision-making, and judgment to determine how to use the claimed invention.

Claims 22-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22, 23, and 30 are confusing in reciting "has a molecular weight of 41K or 38 K as shown in Figure 4." Claim 22 depends upon claim 4. Claim 23 depends upon claim 9. Claim 30 depends upon claim 24. First of all, it is unclear whether this limitation is intended to be a product by process limitation. That is, is the claimed protein intended to be produced in the same manner as those in Figure 4 (see page 5 of the specification) and limited to these specific products? It is noted that each of the lanes is prepared in a different manner. Secondly, claim 9 is directed to a

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protein having the GDF-1 sequence of Figures 2, 11A, or 11B. Dependent claim 23 can be interpreted as being directed to a protein of less than full length because some of the proteins in Figure 4 lack at least the leader sequence. That is, claim 23 would not be properly dependent because it does not contain all of the limitations of the independent claim.

Claims 24-30 are indefinite in that the method contains no clear preamble although it appears to be directed to a method of purification. As written, the single step of "purification" is nebulous as to what method steps are envisioned to achieve purification. It appears that some of the dependent claims implicitly require recombinant production followed by undesignated purification steps.

Applicant's arguments in the preliminary response filed 11/17/97 are not persuasive. Hoban et al. establishes that it was only well after the effective filing date of the invention that the biological activities of this protein were being discovered and assays being developed. There is no statement of use for the protein in the specification as a factor to stimulate immediate early gene expression in neural cell lines. Nothing in the specification would lead one of ordinary skill in the art to this use.

Applicant's specification is an invitation to experiment to determine how to use GDF-1. This specification is analogous to that in Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001, 1005, which was not deemed to be enabling. "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute

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adequate enablement. This specification provides only a starting point, a direction for further research." The specification speculates on possible activities of GDF-1. None of the particular activities disclosed for other TGF- β superfamily members have been shown for this protein. None of the uses set forth in the specification could be practiced at the time of the invention without undue experimentation. Providing a laundry list of potential uses, some of which are diametrically opposed to each other, is not deemed to be enabling.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen, whose telephone number is (703) 308-0666. The examiner can normally be reached on Monday-Friday from 9:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached on (703) 308-3995. Official FAX communications may be directed to either (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Marianne P. Allen
MARIANNE P. ALLEN
PRIMARY EXAMINER
GROUP 1000
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